

REMARKS

Reconsideration of the present application is respectfully requested.

I. Disposition of the claims

Claims 9, 16, 18, and 24 are pending and rejected. Claims 16 and 18 are amended, without prejudice or disclaimer, as shown (~~a biguanide~~ metformin). Support for the amendment is believed obvious from the record and *vide infra*. No new matter is added.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate status identifier.

II. Obviousness Double Patenting (ODP) rejection over claims of USPN 6,677,363

Claims 9, 16, 18, and 24 are rejected over claims 1, 8, 10-11, and 14-15 of the '363 patent under the judicially created doctrine of ODP. Office action, pp. 2-3. The '363 patent issued from application no. 09/937,447, the parent application of the present '738 application. The claims of the '363 patent are shown as Appendix A.

Section 121 states: "A patent issuing on an application with respect to which a requirement for restriction under this section has been made ... shall not be used as a reference either in the [PTO] or in the courts against a divisional application or against the original application or any patent issued on either of them." 35 U.S.C. § 121 (2006).

The present rejection is improper and should be withdrawn, because 35 U.S.C. § 121 shields the present claims from double patenting rejections over the claims of the '363 patent, because (A) the present '738 application is a divisional application of the application that matured into the '363 patent, (B) the '363 patent is one in which a restriction requirement was made during prosecution, and (C) the lines of demarcation made in the restriction requirement of the '447 application have been maintained in the present '738 application.

A. The present '738 application is a divisional application of the application that matured into the '363 patent.

The '363 patent issued from application no. 09/937,447, the parent application of the present '738 application, which claimed domestic priority as a divisional of the '447 application. This information is verifiable from PAIR and the as-filed papers in this '738 application.

B. The '363 patent is one in which a restriction requirement was made during prosecution.

During the prosecution of the '447 application, the present Examiner restricted the claims into three groups as shown in the following image of the Office action:

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-6, 15 and 17 are drawn to an agent and a method of improving ketosis with an insulin sensitizer; and a method of improving ketosis with a composition comprising an insulin sensitizer and insulin, classified in class 514, subclasses 3, 315 and 365.
- II. Claims 7-12, 16 and 18 are drawn to an agent and a method of improving acidosis with an insulin sensitizer; and a method of improving acidosis with a composition comprising an insulin sensitizer and insulin, classified in class 514, subclasses 3, 315 and 365.
- III. Claims 13, 14 and 19 are drawn to an agent and a method for preventing or treating various disorders with an insulin sensitizer, classified in class 514, subclasses 315 and 365.

Office action of 06-21-2002 in the '447 application, p. 2. The present Examiner explained the reasons for restriction as follows:

The three inventions are independent and distinct, each from the other as they have acquired a separate status in the art as shown by their separate subject matter for inventive effort. Further, a reference which anticipates any one of the above inventions would neither anticipate or make obvious of the other inventions. Each such invention is capable of supporting its own patent. For these reasons, the restriction requirement is proper.

Office action of 06-21-2002 in the '447 application, p. 2. In response to the restriction, the claims of Group I were elected and prosecuted to completion, and the claims of Group II, including claim 18, were canceled.

In short, the present Examiner, in no uncertain terms, delineated Group I directed to "a method of treating ketosis" (elected in the '447 application that issued as the '363 patent) from Group II directed to "a method of treating acidosis" (canceled and represented in the present divisional application).

C. The lines of demarcation made in the restriction requirement have been maintained.

As just noted, the present Examiner clearly and unequivocally delineated the claims of the '363 patent from claims directed to "a method of treating acidosis." The Examiner cannot change his position now and use claims directed to "a method of treating ketosis" against the present claims. 35 U.S.C. § 121.

The subject matter of the cited parent '363 patent is a method for improving or treating *ketosis*, while the subject matter of the present '738 application is a method for improving or treating *acidosis*. In the election/restriction requirement issued for the parent patent, the present Examiner judged that these subject matters were independent and distinct. Therefore, Applicants were forced to remove and divide out from the parent patent the subject matter of the present application, i.e., "a method for treating acidosis."

The present rejection which contravenes the previous election/restriction requirement and causes undue damage to the Applicants. It should be withdrawn.

III. 35 U.S.C. § 112, first paragraph, rejection

Claims 9, 16, 18, and 24 are rejected as not being enabled by the present specification. Office action, pp. 3-6. The Examiner agreed that embodiments reciting “metformin” in lieu of “biguanide” have been enabled by the present specification: Office action, p. 3, last paragraph. The present version of the claims have amended, without prejudice or disclaimer, to recite the subject matter that the Examiner considers the specification to have enabled. Therefore, this rejection should be withdrawn.

Conclusion

It is believed that the present application is in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

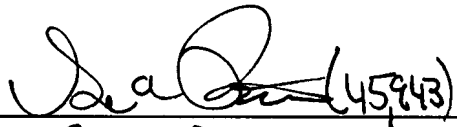
The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 05-01-2007

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Enclosure:
Appendix A: Claims of the '363 patent (2 pages).

APPENDIX A

US 6,677,363 B1

25

3 reveal that an insulin sensitizer (pioglitazone hydrochloride) also improves ketosis caused by diabetes as well as ketosis caused by a biguanide (metformin).
Industrial Applicability

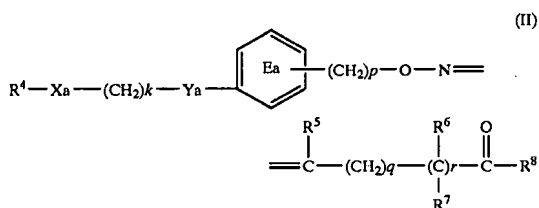
An agent for improving ketosis of the present invention is low in toxicity and useful as an agent for preventing or treating diseases showing ketosis, such as hepatic glycogenosis, endocrine diseases (e.g., hyperthyroidism, acromegaly, pheochromocytoma, glucagonoma), congenital metabolic disorders of carbohydrates or organic acids (e.g., fructose-bisphosphatase deficiency, methylmalonic acidemia, propionic acidemia, isovaleric acidemia, β -ketothiolase deficiency, lacticidemia), acetonemia vomiting or gastrointestinal diseases (e.g., diarrhea).

An agent for improving acidosis of the present invention is low in toxicity and useful as an agent for preventing or treating diseases showing acidosis, such as disturbance of consciousness, coma, respiratory diseases (e.g., pulmonary tuberculosis).

What is claimed is:

1. A method for improving or treating ketosis in a mammal in need thereof, which comprises administering to said mammal an effective amount of an insulin sensitizer selected from the group consisting of

- 1) pioglitazone or a salt thereof,
- 2) a compound of the formula:



wherein R^4 represents a hydrocarbon group that may be substituted or a heterocyclic group that may be substituted; X_a represents a chemical bond, a group of the formula $-\text{CO}-$, $-\text{CH}(\text{OH})-$, or $-\text{NR}^9-$ where R^9 represents hydrogen or an alkyl group that may be substituted; k is an integer of 1 to 3; Y_a represents oxygen atom, sulfur atom, $-\text{SO}-$, $-\text{SO}_2-$, or $-\text{NR}^{10}-$ where R^{10} represents hydrogen or an alkyl group that may be substituted; ring Ea represents a benzene ring that may have further 1 to 3 substituents; p is an integer of 1 to 8; R^5 represents hydrogen, a hydrocarbon group that may be substituted, or a heterocyclic group that may be substituted; q is an integer of 0 to 6; r is 0 or 1; R^8 represents hydroxy, $-\text{OR}^{11}$ where R^{11} represents a hydrocarbon group that may be substituted, or $-\text{NR}^{12}\text{R}^{13}$ where R^{12} and R^{13} are the same or different, and represent hydrogen, a hydrocarbon group that may be substituted, a heterocyclic group that may be substituted, or an acyl group that may be substituted, or R^{12} and R^{13} may be combined to form a ring; R^6 and R^7 are the same or different, and represent hydrogen or a hydrocarbon group that may be substituted, or R^6 and R^5 may be combined to form a ring; or a salt thereof;

- 3) 5-[[6-(2-fluorobenzoyloxy)-2-naphthyl]methyl]-2,4-thiazolidinedione;
- 4) FK-614; and
- 5) KRP-297.

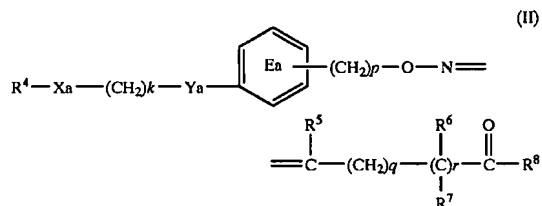
2. The method of claim 1 wherein the insulin sensitizer is pioglitazone hydrochloride.

3. The method of claim 1 wherein the ketosis is diabetic ketosis.

26

4. The method of claim 1 which is for treating hepatic glycogenosis, endocrine diseases, congenital metabolic disorders of carbohydrates or organic acids, acetonemia, vomiting or gastrointestinal diseases.

5. The method of claim 1 wherein the insulin sensitizer is a compound of the formula:



wherein R^4 represents a hydrocarbon group that may be substituted or a heterocyclic group that may be substituted; X_a represents a chemical bond, a group of the formula $-\text{CO}-$, $-\text{CH}(\text{OH})-$, or $-\text{NR}^9-$ where R^9 represents hydrogen or an alkyl group that may be substituted; k is an integer of 1 to 3; Y_a represents oxygen atom, sulfur atom, $-\text{SO}-$, $-\text{SO}_2-$, or $-\text{NR}^{10}-$ where R^{10} represents hydrogen or an alkyl group that may be substituted; ring Ea represents a benzene ring that may have further 1 to 3 substituents; p is an integer of 1 to 8; R^5 represents hydrogen, a hydrocarbon group that may be substituted, or a heterocyclic group that may be substituted; q is an integer of 0 to 6; r is 0 or 1; R^8 represents hydroxy, $-\text{OR}^{11}$ where R^{11} represents a hydrocarbon group that may be substituted, or $-\text{NR}^{12}\text{R}^{13}$ where R^{12} and R^{13} are the same or different, and represent hydrogen, a hydrocarbon group that may be substituted, a heterocyclic group that may be substituted, or an acyl group that may be substituted, or R^{12} and R^{13} may be combined to form a ring; R^6 and R^7 are the same or different, and represent hydrogen or a hydrocarbon group that may be substituted, or R^6 and R^5 may be combined to form a ring; or a salt thereof.

6. The method of claim 5, wherein the compound is
 - Z-2-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-2-phenylacetic acid;
 - Z-4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-4-phenylbutyric acid;
 - Z-2-(4-bromophenyl)-2-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]acetic acid;
 - Z-2-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-2-(4-phenoxyphenyl)acetic acid;
 - Z-4-(4-fluorophenyl)-4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]butyric acid;
 - Z-3-methyl-2-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]butyric acid;
 - E-4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-4-phenylbutyric acid;
 - E-4-(4-fluorophenyl)-4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]butyric acid;
 - E-4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-4-phenylbutyramide; or
 - E-8-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-8-phenyloctanoic acid.

7. The method of claim 1 wherein said ketosis is caused by a biguanide.

8. The method of claim 1 further comprising administering insulin to said mammal.

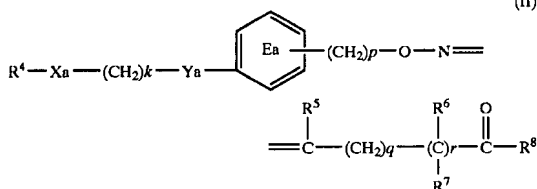
9. A method for improving or treating ketosis which comprises administering an effective amount of an insulin sensitizer in combination with insulin to a mammal in need thereof.

US 6,677,363 B1

27

10. The method of claim 9 wherein the insulin sensitizer is selected from the group consisting of

- 1) pioglitazone or a salt thereof,
- 2) a compound of the formula:

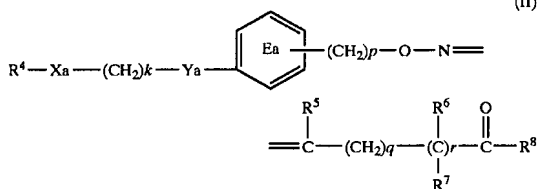


wherein R^4 represents a hydrocarbon group that may be substituted or a heterocyclic group that may be substituted; Xa represents a chemical bond, a group of the formula $-\text{CO}-$, $-\text{CH}(\text{OH})-$, or $-\text{NR}^9-$ where R^9 represents hydrogen or an alkyl group that may be substituted; k is an integer of 1 to 3; Ya represents oxygen atom, sulfur atom, $-\text{SO}-$, $-\text{SO}_2-$, or $-\text{NR}^{10}-$ where R^{10} represents hydrogen or an alkyl group that may be substituted; ring Ea represents a benzene ring that may have further 1 to 3 substituents; p is an integer of 1 to 8; R^5 represents hydrogen, a hydrocarbon group that may be substituted, or a heterocyclic group that may be substituted; q is an integer of 0 to 6; r is 0 or 1; R^8 represents hydroxy, $-\text{OR}^{11}$ where R^{11} represents a hydrocarbon group that may be substituted, or $-\text{NR}^{12}\text{R}^{13}$ where R^{12} and R^{13} are the same or different, and represent hydrogen, a hydrocarbon group that may be substituted, a heterocyclic group that may be substituted, or an acyl group that may be substituted, or R^{12} and R^{13} may be combined to form a ring; R^6 and R^7 are the same or different, and represent hydrogen or a hydrocarbon group that may be substituted, or R^6 and R^5 may be combined to form a ring; or a salt thereof;

- 3) 5-[[6-(2-fluorobenzyloxy)-2-naphthyl]methyl]-2,4-thiazolidinedione;
- 4) FK-614; and
- 5) KRP-297.

11. The method of claim 10 wherein the insulin sensitizer is pioglitazone hydrochloride.

12. The method of claim 10, wherein the insulin sensitizer is a compound of the formula:



wherein R^4 represents a hydrocarbon group that may be substituted or a heterocyclic group that may be substituted;

28

Xa represents a chemical bond, a group of the formula $-\text{CO}-$, $-\text{CH}(\text{OH})-$, or $-\text{NR}^9-$ where R^9 represents hydrogen or an alkyl group that may be substituted; k is an integer of 1 to 3; Ya represents oxygen atom, sulfur atom, $-\text{SO}-$, $-\text{SO}_2-$, or $-\text{NR}^{10}-$ where R^{10} represents hydrogen or an alkyl group that may be substituted; ring Ea represents a benzene ring that may have further 1 to 3 substituents; p is an integer of 1 to 8; R^5 represents hydrogen, a hydrocarbon group that may be substituted, or a heterocyclic group that may be substituted; q is an integer of 0 to 6; r is 0 or 1; R^8 represents hydroxy, $-\text{OR}^{11}$ where R^{11} represents a hydrocarbon group that may be substituted, or $-\text{NR}^{12}\text{R}^{13}$ where R^{12} and R^{13} are the same or different, and represent hydrogen, a hydrocarbon group that may be substituted, a heterocyclic group that may be substituted, or an acyl group that may be substituted, or R^{12} and R^{13} may be combined to form a ring; R^6 and R^7 are the same or different, and represent hydrogen or a hydrocarbon group that may be substituted, or R^6 and R^5 may be combined to form a ring; or a salt thereof.

13. The method of claim 12 wherein the compound is

- Z-2-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-2-phenylacetic acid;
- Z-4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-4-phenylbutyric acid;
- Z-2-(4-bromophenyl)-2-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]acetic acid;
- Z-2-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-2-(4-phenoxyphenyl)acetic acid;
- Z-4-(4-fluorophenyl)-4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]butyric acid;
- Z-3-methyl-2-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]butyric acid;
- E-4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-4-phenylbutyric acid;
- E-4-(4-fluorophenyl)-4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]butyric acid;
- E-4-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-4-phenylbutyramide; or
- E-8-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyloxyimino]-8-phenyloctanoic acid.

14. The method of claim 9 wherein the ketosis is diabetic ketosis.

15. The method of claim 9 wherein said ketosis is caused by a biguanide.

16. The method of claim 9 which is for treating hepatic glycogenosis, endocrine diseases, congenital metabolic disorders of carbohydrates or organic acids, acetonemia, vomiting or gastrointestinal diseases.

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